BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

(12) INTERNATIONAL [redacted]LICATION PUBLISHED UNDER THE PATEN[redacted]OOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 February 2001 (22.02.2001)

PCT

(10) International Publication Number
WO 01/12156 A1

(51) International Patent Classification[7]: A61K 9/00

(21) International Application Number: PCT/US00/19549

(22) International Filing Date: 26 July 2000 (26.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/148,508 12 August 1999 (12.08.1999) US

(71) Applicant *(for all designated States except US)*: **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KASSEBAUM, James, Web** [US/US]; 9221 Leeward Court, Indianapolis, IN 46256 (US). **PUGH, Paul, Thomas** [US/US]; 8312 South Mill Road, Knightstown, IN 46148 (US). **THOMPSON, William, Webster** [US/US]; 5521 Overbrook Circle, Indianapolis, IN 46226 (US).

(74) Agents: **DEMETER, John, C.** et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/12156 A1

(54) Title: TOPICAL ORGANIC ECTOPARASITICIDAL FORMULATIONS

(57) Abstract: This invention provides topical ectoparasiticidal formulations comprising an ectoparasiticide, preferably a pyrethroid or a spinosyn, a spreading agent that is a (C_3-C_6) branched alkyl (C_{10}-C_{20}) alkanoate, preferably isopropyl myristate, and optionally a miscibilizing agent compatible with organic solvent systems, and methods of controlling an ectoparasite infestation on certain animals comprising topically applying such formulations to the animal.

TOPICAL ORGANIC ECTOPARASITICIDAL FORMULATIONS

This invention relates to topical organic ectoparasiticidal formulations. Ectoparasites such as fleas, blowflies, lice, ticks and mites can seriously affect productivity in the domesticated animal industries. Further, such parasites cause disease and discomfort for pets and other companion animals. Ectoparasites are often controlled by topically applying an insecticide or mixture of insecticides onto the animal. Topical ectoparasite control agents are usually applied in liquid formulations. The formulations can be applied by spot-on application, plunge or spray dipping, jetting with a hand held spray or in a race, or as a back-line spray or pour-on.

A particular problem with topical formulations is poor migration from the site of application. In the sheep industry, for example, treatment for ectoparasites is commonly carried out in the early season within 24 hours after shearing, or, less frequently, later in the season when the wool is longer. Especially with early season treatments, when the topical formulation is applied along the dorsal midline or back-line of the animal, the insecticide component of currently available commercial formulations migrates very poorly from the application site. Typically less than 10% of the applied insecticide diffuses away from the application site within the first 10 days. Thus, extensive areas of the animal's skin and/or hair may receive sublethal concentrations of the insecticide. These areas remain susceptible to damaging invasion by ectoparasites.

To overcome the inadequate control caused by poor migration of the insecticide, it has become common in the industry to apply relatively large amounts of insecticide. This practice introduces unwelcome costs, results in the presence of insecticide residues in certain animal products (such as wool and wool byproducts) and increases the potential of environmental pollution. It also increases the risk of unwanted and unnecessary exposure to pesticides to animal handlers and farmers treating the animals.

Solvent-based formulations have received attention in recent times in the search for greater insecticide mobility that would allow the same insecticidal effect to be achieved with less insecticide in the formulations. Up to the present, there

has been little success in identifying a solvent that materially enhances the spread of insecticides that are applied using a spot-on or pour-on method.

This invention provides insecticidal formulations that can be applied topically to animals and that have the advantage of permitting the active ingredient to spread over the surface of the skin and/or hair of the treated animal, thereby providing more extensive coverage of the insecticide. These formulations, therefore, provide greater inhibition or eradication of ectoparasites with smaller amounts of insecticide.

The topical ectoparasiticidal formulations of this invention comprise an ectoparasiticide, a spreading agent and optionally a miscibilizing agent. More specifically, the invention relates to a topical ectoparasiticidal formulation comprising from about 0.1 to about 25 weight percent of an ectoparasiticide, from about 25 to about 99.9 weight percent of a (C_3-C_6) branched alkyl (C_{10}-C_{20}) alkanoate spreading agent, and optionally up to about 70 weight percent of a miscibilizing agent compatible with organic solvent systems.

An exemplary topical ectoparasiticidal formulation of this invention is one wherein the ectoparasiticide is a spinosyn, or a physiologically acceptable derivative or salt thereof.

This invention also encompasses a method of controlling an ectoparasite infestation on a small ruminant or companion animal, comprising topically applying to the hair and/or skin of the animal a formulation comprising from about 0.1 to about 25 weight percent of a spinosyn, or a physiologically acceptable derivative or salt thereof, from about 25 to 99.9 weight percent isopropyl myristate, and from 0 to about 70 weight percent of a miscibilizing agent compatible with organic solvent systems.

The invention also relates to an article of manufacture, comprising packaging material and a topical formulation for controlling an ectoparasite infestation on a small ruminant or companion animal contained within said packaging material, wherein said formulation comprises

a topical unit dose of a formulation comprising 0.1 to about 25 weight percent of an ectoparasiticide, from about 25 to about 99.9 weight percent of a (C_3-C_6) branched alkyl (C_{10}-C_{20}) alkanoate spreading

agent, and optionally up to about 70 weight percent of a miscibilizing agent compatible with organic solvent systems; and,

wherein said packaging material comprises a label or package insert with instructions for topically administering the dose to the animal.

This article of manufacture or kit is particularly appropriate when the companion animal is a dog or a cat. The timing of administering the doses will generally be every 30 days. Each kit typically contains a sufficient number of doses to control the ectoparasite infestation for a period of several months.

This invention further provides a topical formulation for controlling an ectoparasite infestation on a small ruminant or companion animal comprising a spinosyn, or a derivative or salt thereof, and a spreading agent substantially as hereinbefore described with references to any one of the Examples.

Examples of small ruminant animals are a sheep, a goat or a camellid.

The term "companion animal" includes dogs, cats, horses and other pets owned and maintained in close association with humans as part of the human-animal bond.

The term "controlling" as used herein refers to either ameliorating or eliminating a current infestation or preventing an infestation in a susceptible host.

Many insecticidal agents are useful in the formulations of this invention. Indeed, any ectoparasiticidal compound that is soluble in a (C_3-C_6) branched alkyl (C_{10}-C_{20}) alkanoate vehicle and is useful for topical application can be incorporated as the insecticidal component of these formulations. Typically, the insecticidal agent is active against a broad spectrum of pest species, including acaricides, antiparasitic agents, insect growth regulators and compounds that inhibit or kill flies, flying pests and other "temporary" pests that only alight momentarily on domesticated animals.

Examples of useful classes of insecticides are spinosyns, organophospates, organochlorines, carbamates, and pyrethrins. Specific useful insecticidal compounds include tetraethyl pyrophosphate (TEPP), mevinphos, disulfoton, azinphosmethyl, parathion, methylparathion, chlorfenvinphos, cichlorvos, diazinon, dimethoate, trichlorfon, chlorothion, malathion, ronnel, abate, baygon, carbaryl, mobam, temik, zectran, methoxychlor, aldrin, dieldrin, endrin, heptachlor,

chlordane, lindane, mirex, nicotine, rotenoids, pyrethrums, spinosyns and synthetic pyrethroids, including cypermethrin.

Preferred insecticides useful in these formulations are spinosyns or a pyrethroid such as cypermethrin.. Spinosyns are especially preferred.

The spinosyns (also known as A83453 factors) are agricultural insecticides that have shown activity against southern armyworm and other insects in the order *Lepidoptera*, and cotton aphid and other members of the order *Homoptera*. (See, for example, U.S. Patent No. 5,571,901).

The spinosyns were also known to have some ectoparasiticidal activity, i.e., they had *in vitro* activity against mosquito larvae, black blowfly larvae and adult stable flies, which are members of the insect order *Diptera*, and transient systemic activity against larval blowfly and adult stable fly in guinea pigs and sheep. For these tests, the spinosyns were administered in aqueous polyvinylpyrrolidone or in polyethylene glycol (see U.S. Patent No. 5,571,901, col. 26-32).

The spinosyns are naturally-derived macrolides produced by fermentation of *Saccharopolyspora spinosa*. The fermentation produces multiple factors, including spinosyn A and spinosyn D (also called A83543A and A8354D). Spinosyn A and spinosyn D are the two spinosyns that are most active as insecticides. An agricultural product comprised mainly of these two spinosyns is available commercially under the name "spinosad".

Spinosyn A was the first spinosyn isolated and identified from the fermentation broth of *Saccharopolyspora spinosa*. Subsequent examination of the fermentation broth revealed that *S. spinosa* produced a number of spinosyns that have been called spinosyns A to H and J. Additional spinosyns, denominated K to W, have been identified from various strains of *S. spinosa*. The various spinosyns are characterized by differences in the substitution patterns on the amino group of the forosamine, at selected sites on the tetracyclic ring system and on the 2N,3N,4N-(tri-O-methyl)rhamnose group.

Boeck et al. described spinosyns A-H and J (which they called A83543 factors A, B, C, D, E, F, G, H and J), and salts thereof, in U.S. Patent Nos. 5,362,634 (issued Nov. 8, 1994); 5,496,932 (issued March 5, 1996); and 5,571,901 (issued Nov. 5, 1996). Mynderse et al. described spinosyns L-N (which they called A83543

factors L, M and N), their N-dimethyl derivatives, and salts thereof, in U.S. Patent No. 5,202,242 (issued Apr. 13, 1993); and Turner et al. described spinosyns Q-T (which they called A83543 factors Q, R, S and T), their N-dimethyl derivatives, and salts thereof, in U.S. Patent Nos. 5,591,606 (issued January 7, 1997) and 5,631,155 (issued May 29, 1997). Spinosyns K, O, P, U, V, W and Y are described, for example, by Carl V. DeAmicis, James E. Dripps, Chris J. Hatton and Laura I. Karr in American Chemical Society's Symposium Series: Phytochemicals for Pest Control, Chapter 11, "Physical and Biological Properties of Spinosyns: Novel Macrolide Pest-Control Agents from Fermentation", pages 146-154 (1997).

The spinosyns can be isolated in the form of salts that are also useful in the formulations of this invention. The salts are prepared using standard procedures for salt preparation. For example, spinosyn A can be neutralized with an appropriate acid to form an acid addition salt. Representative suitable acid addition salts include salts formed by reaction with either an organic or inorganic acid, for example, sulfuric, hydrochloric, phosphoric, acetic, succinic, citric, lactic, maleic, fumaric, cholic, pamoic, mucic, glutamic, camphoric, glutaric, glycolic, phthalic, tartaric, formic, lauric, stearic, salicylic, methanesulfonic, benzenesulfonic, sorbic, picric, benzoic, cinnamic and like acids.

The term a "spinosyn or a derivative thereof" as used herein refers to an individual spinosyn factor (spinosyn A, B, C, D, E, F, G, H, J, K, L, M, N, O, P, Q, R, S, T, U, V, W or Y), an N-dimethyl derivative of one or more spinosyn factor, or a combination thereof. For convenience, the term "spinosyn component" as used means an individual spinosyn or a physiologically acceptable derivative or salt thereof, or a combination thereof. "Spinosad" as used herein refers to a mixture of spinosyns comprised mainly of spinosyns A and D.

The spinosyns are known to have excellent human and animal safety and toxicological profiles. Because of their low toxicity to animals and humans, spinosyns are considered to be environment-friendly, "green" insecticides. It is desirable to formulate spinosyns to maintain this "green" profile.

Spinosyns have recently been found to be useful in the eradication or control of ectoparasites on sheep and companion animals. Thus, formulations of

spinosyns with low toxicity and increased stability are potentially valuable in combating ectoparasites and the diseases such pests often carry.

The present formulations further comprise a (C_3-C_6) branched alkyl (C_{10}-C_{20}) alkanoate. This component is an organic solvent that acts as a spreading agent. Spreading agents increase the spreading of, and aid in substantially equalizing the distribution of, the active ingredient over the hair and/or skin surface area of the animal over time. The spreading agent solvent system should be safe, non-toxic, environment-friendly and non-flammable.

The branched alkyl portion of the (C_3-C_6) branched alkyl (C_{10}-C_{20}) alkanoate includes all branched chain isomers of C_3-C_6 alkyl groups. Examples are isopropyl, isobutyl, isopentyl, and isohexyl. The (C_{10}-C_{20}) alkanoate moiety includes all C_{10}-C_{20} fatty alkanoate groups, including but not limited to, decanoate (C_{10}), hendecanoate (C_{11}), dodecanoate (C_{12}), tridecanoate (C_{13}), tetradecanoate (C_{14}), pentadecanoate (C_{15}), hexadecanoate (C_{16}), heptadecanoate (C_{17}), octadecanoate (C_{18}), and eicosanoate (C_{20}). Preferably, the spreading agent is a (C_3-C_6) branched alkyl (C_{12}-C_{16}) alkanoate. Of these solvents, C_3- branched alkyl-C_{14} alkanoates are especially useful. A preferred spreading agent is isopropyl myristate (IPM).

The formulations can optionally contain a miscibilizing agent. The miscibilizing agent aids in solubilizing the active ingredient and must be compatible with organic solvent systems. The phrase "compatible with organic solvent systems" means that the miscibilizing agent does not form more than one phase when mixed with the (C_3-C_6) branched alkyl (C_{10}-C_{20}) alkanoate component.

Suitable miscibilizing agents for use in these formulations generally are (C_1-C_{30}) organic acids. Typically, such organic acids are straight-chain saturated fatty acids, but they can also be low molecular weight organic acids such as formic acid, acetic acid, propionic acid and benzoic acid.

The choice of miscibilizing agent will vary depending on the insecticide in the formulation. When the insecticide component is a spinosyn, examples of suitable miscibilizing agents are formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, enanthic acid, caprylic acid, pelargonic acid, capric acid, undecylic acid, lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid, oleic, arachidic acid, behenic acid,

lignoceric acid, cerotic acid, montanic acid, triacontanoic acid, psyllic acid, and ceroplastic acid. Other useful miscibilizing agents are (C_1-C_{30}) alkyl sulfuric acids, (C_1-C_{30}) alkyl phosphoric acids, and (C_1-C_{30}) alkyl sulfonic acids.

In formulations containing a spinosyn solubilized in isopropyl myristate, for example, oleic acid is a particularly useful miscibilizing agent because it aids in solubilizing the spinosyn (thus allowing for the formation of solvent solutions containing relatively high concentrations of active ingredient), and it is compatible with the isopropyl myristate component.

Compounds other than (C_1-C_{30}) organic acids can also be useful miscibilizing agents in the formulations of this invention. In general, a miscibilizing compound useful for these formulations: 1) is compatible with the selected organic solvent component, and 2) solubilizes the active ingredient without substantially altering the spreading properties of the formulation.

When insecticide is a spinosyn and the spinosyn component is spinosyn D or spinosad (i.e., a mixture of spinosyns A and D), it is especially important that the miscibilizing agent is able to solubilize the spinosyn D sufficiently. In technical grade spinosad, factor D is generally the factor that causes solubility problems when preparing spinosad-containing formulations. Examples of miscibilizing agents that are useful for spinosad-containing ectoparasiticidal formulations of the present invention include, but are not limited to, benzyl alcohol, ethylene glycol phenyl ether, D-limonene, N-methyl-2-pyrrolidinone, and methylated soybean oils and soybean oil methyl esters, such as SOYGOLD 1000 (AG Environmental Products LLC).

The present formulations can also contain other optional ingredients, such as: antioxidants, UV-absorbing compounds or photostabilizers, viscosity-modifying agents, antimicrobial agents, dyes, perfumes, deodorants and physiologically or dermatologically acceptable carriers, diluents, excipients or adjuvants. Such agents are known in the art.

For example, one or more antioxidants can be added to the formulations in an amount effective to retard oxidation of the formulation components and the ensuing degradative effects. Potentially useful antioxidants include primary

antioxidants that are radical scavengers, such as hindered phenolics and secondary amines, and secondary antioxidants, such as phosphites and thioesters that function as peroxide decomposers. Preferred antioxidants for use in these formulations are blends of primary and secondary antioxidants, including particularly blends of phenolic and phosphite antioxidant compositions.

There are many commercially available antioxidants products designed for polymer stabilization, including antioxidant formulations comprising synergistic combinations of primary and secondary antioxidants. Examples of commercially available antioxidants useful in the formulations of this invention include the Irganox® antioxidants available from Ciba Geigy, Vanox® antioxidants from R.T. Vanderbilt, and the Naugard® antioxidants available from Uniroyal Chemicals.

When the formulations include an antimicrobial component, it should be present in an amount effective to prevent the growth of microorganisms in the formulation.

Generally, the formulations of this invention can be prepared by blending the components with adequate mixing or stirring. For example, a useful spinosad formulation is one having a final concentration of 2 mg of spinosad per mL. One such formulation is prepared to contain 99.1 weight percent IPM, 0.6 weight percent oleic acid, and 0.3 weight percent spinosad technical (89% active ingredient). This formulation is made by adding the appropriate amount of spinosad to the IPM solvent with mixing or stirring, blending the oleic acid into the IPM/spinosad mixture, and continuing the mixing or stirring until the spinosad has completely solubilized to form the final formulation product. An optional additional step is to filter the final formulation to remove any impurities or extraneous materials.

The formulations of this invention are applied to the animal topically. Topical control protocols include spot-on or pour-on treatments wherein the formulation is placed directly onto a discreet skin and/or hair surface area of the animal and allowed to spread over the remainder of the animal's skin or hair surface area. Generally, spot-on or pour-on protocols involve initially placing the formulation on the dorsal midline (i.e., the head, neck, shoulders or back) of the animal. Placement typically occurs on a dorsal midline surface area that constitutes less than 10% of the animal's entire surface area. For example, a typical pour-on treatment

protocol involves applying about 4 to about 50 mL of a liquid ectoparasiticidal formulation in a narrow strip along the backline of an animal, from the withers to the tail or rump.

For spot-on or pour-on treatment to control ectoparasites, such as lice, which are present over the whole surface of an animal, the ectoparasiticidal active ingredient must spread from the narrow strip at the backline to cover the entire surface of the animal. The present formulations have this advantageous spreading effect. Of course, they can be applied to areas of skin that constitute greater than 10% of the surface area of the animal, but such applications limit the advantage offered by these formulations. Another advantage of these formulations is that they offer extended ectoparasiticidal coverage and need not be applied more than weekly or biweekly at most.

Example 1

Wetting Tests for Various Solvent Systems

To determine organic solvents that are useful spreading agents, solvent systems that are capable of solubilizing at least 1% spinosad by weight percent were screened for hair wetting by applying about 1 mL of the solvent system (solvents were screened without active ingredient), dropwise, to a tanned rabbit pelt that was at an angle of about 45°. Solvent systems that wet the rabbit hair and did not run off before wetting the hair were considered to pass the screen. Table I describes the ability of selected organic solvents to wet the rabbit hair.

Table I. Ability of Solvents and Aqueous Surfactant Systems to Wet Rabbit Hair on Tanned Rabbit Pelts.

Organic Solvent	
Wet Well	**Did Not Wet**
isopropyl myristate	triacetin
methyl laurate	N-methyl pyrrolidone
dipropylene glycol methyl ether	propylene glycol
butyl lactate	
methyl caprate	
methyl oleate	
octanoic acid	
limonene	
hexanol	
ethyl oleate	

As Table I shows, water immiscible, nonpolar solvents generally wet well, although dipropylene glycol methyl ether is water miscible and did wet the hair very well.

Example 2

Formulation Spreading Tests

Further studies were conducted to determine the abilities of various solvents to aid in spreading of active ingredient.

International Patent Application WO 9524219 teaches that wool grease fraction (F1) provides superior spreading of pyrethroid insecticides on sheep when compared to organic solvent spreading agents. Tests were conducted to compare the spreading properties of formulations containing the F1 wool grease fraction and various organic solvents. The amount and rate of diffusion of ^{14}C-labeled zeta-cypermethrin from the dorsal midline of sheep were determined when applied in F1 wool grease fraction and a range of test excipients. Four formulations containing 10

mg/mL zeta-cypermethrin spiked with 100 μCi [^{14}C] zeta-cypermethrin were prepared in the following vehicles: wool grease fraction F1, isopropyl myristate, octyl stearate and glyceryl tricaprylate/caprate. A dose of 1 mL/5kg body weight of each formulation was applied to the backline of 3 sheep. Wool was collected and pooled 1, 2, 4, 8, 11 and 14 days after treatment from three 12 x 12 mm squares chosen at random, along meridian lines drawn 2, 7.5 and 15 cm down the side of each sheep from the backline. The clipped areas were also swabbed. At day 14 after treatment the wool at the site of application was collected, and back and perirenal fat samples were collected. The quantity of zeta-cypermethrin in each sample was measured by liquid scintillation counting.

For the majority of the measurements taken, isopropyl myristate gave the greatest spread of zeta-cypermethrin and the wool grease fraction F1 provided the least spreading. When the vehicle was the F1 wool grease fraction, only the 2-cm meridian showed increased concentration of zeta-cypermethrin over time after initial application. When the vehicle was isopropyl myristate, the quantity of zeta-cypermethrin measured at all meridians increased with time following administration. Octyl stearate and glyceryl tricaprylate/caprate gave modest spread, but not as great as the spread provided by the IPM formulations. Tissue residues were similar amongst formulations except the glyceryl tricaprylate/caprate formulation appeared to cause the highest residue levels.

After two weeks it was determined that F1 was a comparatively poor spreading agent, octyl stearate and glyceryl tricaprylate/caprate provided better spreading properties, and isopropyl myristate gave the best spread of zeta-cypermethrin.

Example 3

Ectoparasiticidal Efficacy Tests of Wool Grease and IPM Formulations

Tests were conducted to compare the efficacy of formulations of spinosad in F1 wool grease fraction versus those in isopropyl myristate against lice on sheep. Two F1 formulations containing spinosad at 2 mg/mL and 10 mg/mL, and one formulation containing 2 mg/mL spinosad in isopropyl myristate were made as follows:

a) F1 Formulation (2 mg/mL)

81.11 % F1
18.62 % solvent (50/50 petroleum ether/acetone)
0.27 % spinosad technical that was 89% active
100 % (w/w)

Formulation density = 0.84 g/mL

b) F1 Formulation (10 mg/mL)

80.26 % F1
18.42 % solvent (50/50 petroleum ether/acetone)
1.32 % spinosad technical that was 89% active
100 %

Formulation density = 0.84 g/mL

c) IPM Formulation (2 mg/mL)

99.123 % IPM
0.613 % oleic acid
0.264 % spinosad technical that was 89% active
100 %

Formulation density = 0.85 g/mL

Each formulation was administered to sheep as a pour-on application immediately after shearing. Spinosad/F1 formulations were tested at doses of 0 (i.e., vehicle alone), 0.4 and 2 mg/kg, while the spinosad/IPM formulation was tested at a dose of 0.4 mg/kg. The 2 mg/kg dose of spinosad/F1 was administered using the 10 mg/mL formulation, while the 0.4 mg/kg doses were administered using the 2 mg/mL formulations. Lice counts were taken on the sheep at sites all over the animal, including the head and neck. These lice counts were taken before treatment and on or about weekly for the following eight weeks. The results of this study are summarized in Table II.

Table II: Comparison of Ectoparasiticidal Efficacy of Spinosad in F1 and IPM Formulations in Sheep
Lice Counts (mean)

		Week of Study							
	Day 0 lice count	1	2	3	4	5	6	7	8
F1 Only	643	428	328	350	237	245	159	156	145
0.4 mg/kg Spinosad/F1	622	391	213	211	159	118	103	69	68
2 mg/kg Spinosad/F1	582	146	86	48	2	13	4	3	2
0.4 mg/kg Spinosad/IPM	575	138	81	68	47	32	13	25	21

As the results summarized in Table II show, spinosad in IPM at a dose of 0.4 mg/kg was superior in lice control to spinosad in F1 at 0.4 mg/kg, and was almost equal in efficacy to spinosad in F1 at 2 mg/kg. Spinosad in IPM gave outstanding control of lice on sheep, including control of lice on the head and neck, which indicated that IPM potentiated the spreading of spinosad from the dorsal midline to the head, neck and other body surface regions.

Example 4

Efficacy of Spinosad in Various Organic Solvents vs. Lice in Sheep

Further lice efficacy studies on sheep were conducted to compare the efficacy of IPM as a spreading agent to that of other organic solvent systems containing blends of organic solvents. The formulations tested had the following compositions:

a) IPM Formulation:
99.12 % IPM
0.61 % oleic acid
0.27 % spinosad technical (89% active)

b) OP/IPM Formulation
79.78% octyl palmitate (OP)
19.95% IPM
0.27% spinosad technical (89% active)

c) GTCC/OP Formulation
79.78% glyceryl tricaprylate/caprate (GTCC)
19.95% octyl palmitate
0.27% spinosad technical (89% active)

d) GTCC/IPM/CAP Formulation
69.81% glyceryl tricaprylate/caprate
14.96% IPM
14.96% cetearyl octanoate (CAP)
0.27% spinosad technical (89% active)

e) OP/IPM/OSU Formulation
69.81% octyl palmitate
14.96% IPM
14.96% dioctyl succinate (OSU)
0.27% spinosad technical (89% active)

f) TPM/LWG/GTCC Formulation
59.84% tripropylene glycol methyl ether (TPM)
19.95% liquid wool grease (LWG)
19.95% glyceryl tricaprylate/caprate
0.27% spinosad technical (89% active)

g) TPM/OSU Formulation
79.78% tripropylene glycol methyl ether
19.95% dioctyl succinate
0.27% spinosad technical (89% active)

Lice counts were taken on the sheep at sites all over the animal, including the head and neck. These lice counts were taken before treatment and on or about weekly for the following twelve weeks. The results of this study summarized in Table III.

Table III: Efficiacy of Spinosad in Organic Solvent Formulations vs. Lice in Sheep

Lice Count (mean)

		Weeks					
Treatment	Pretreatment lice count	1	2	4	6	8	12
Control	253	197	128	163	206	162	204
IPM	268	33	23	18	20	18	18
OP/IPM	271	71	51	83	90	71	184
GTCC/OP	257	32	28	40	52	46	106
GTCC/IPM/CAP	278	28	16	24	25	22	33
OP/TPM/OSU	259	33	19	23	22	19	40
TM/LWG/GTCC	267	53	29	39	34	27	48
TPM/OSU	259	58	38	64	62	66	119

As Table III shows, spinosad in IPM alone was the most effective treatment of the 7 formulations tested. A strong correlation exists between the results of the spreading experiments and those of the field efficacy experiments. Spinosad formulations in IPM exhibited excellent spreading characteristics and demonstrated outstanding long-term protective and inhibitory effects against ectoparasiticidal infestation in sheep.

Examples 5-11 illustrate various formulations of this invention.

Example 5: Spinosad/IPM/acetic acid Formulation

5.65% spinosad (88.5% active)
3% acetic acid
91.35% IPM

Example 6: Spinosad/IPM/octanoic acid Formulation

5.65% spinosad (88.5% active)
7.5% octanoic acid
86.85% IPM

Example 7: Spinosad/IPM/lauric acid Formulation
5.65% spinosad (88.5% active)
10.15% lauric acid
84.2% IPM

Example 8: Spinosad/IPM/oleic acid Formulation
5.65% spinosad (88.5% active)
16.5% oleic acid
77.85% IPM

Example 9: Spinosad/IPM/benzoic acid Formulation
5.65% spinosad (88.5% active)
3.76% benzoic acid
90.59% IPM

Example 10: Spinosad/IPM/NMP Formulation
5.65% spinosad (88.5% active)
40.0% 1-methyl-2-pyrrolidinone (NMP)
54.35% IPM

Example 11: Zeta-cypermethrin/IPM Formulation
1.18% zeta-cypermethrin (84.7% active)
98.82% IPM

The formulations of Examples 5-10 can be prepared by weighing the spinosad into a suitable container, adding the IPM and stirring to create a slurry, and then adding the final component and stirring until a clear solution is achieved. In preparing the formulation of Example 11, the zeta-cypermethrin is an oily liquid that requires gentle heating (approximately 40-50°C) to allow for proper mixing into the organic solvent phase. No separation of phases is evident upon cooling.

CLAIMS

1. A topical ectoparasiticidal formulation comprising from about 0.1 to about 25 weight percent of an ectoparasiticide, from about 25 to about 99.9 weight percent of a (C_3-C_6) branched alkyl (C_{10}-C_{20}) alkanoate spreading agent, and optionally up to about 70 weight percent of a miscibilizing agent compatible with organic solvent systems.

2. A formulation of Claim 1 wherein the spreading agent is a (C_3-C_6) branched alkyl (C_{12}-C_{16}) alkanoate.

3. A formulation of Claim 2 wherein the (C_3-C_6) branched alkyl (C_{10}-C_{20}) alkanoate is isopropyl myristate.

4. A formulation of Claim 1, 2 or 3 wherein the ectoparasiticide is a spinosyn, or a physiologically acceptable derivative or salt thereof.

5. A formulation of Claim 1, 2 or 3 wherein the ectoparasiticide is cyperpyrethrin.

6. A formulation of Claim 1, 2, 3, 4 or 5 which further comprises a miscibilizing agent selected from formic, acetic, propionic, benzoic, butyric, valeric, caproic, benzoic, enanthic, caprylic, pelargonic, capric, undecylic, lauric, tridecylic, myristic, pentadecylic, palmitic, margaric, stearic, oleic, arachidic, behenic, lignoceric, cerotic, montanic, triacontanoic, psyllic, or ceroplastic acids.

7. A formulation of Claim 1, 2, 3, 4 or 5 which further comprises a miscibilizing agent selected from benzyl alcohol, ethylene glycol phenyl ether, D-limonene, N-methyl-2-pyrrolidinone, methylated soybean oils and soybean oil methyl esters.

8. A formulation of Claim 1, 2, 3, 4, 5, 6 or 7 which further comprises an effective amount of an antimicrobial agent.

9. An article of manufacture, comprising packaging material and a topical formulation for controlling an ectoparasite infestation on a small ruminant or companion animal contained within said packaging material, wherein said formulation comprises

a topical unit dose of a formulation of Claim 1, 2, 3, 4, 5, 6, 7 or 8; and,

wherein said packaging material comprises a label or package insert with instructions for topically administering the dose to the animal.

10. A method of controlling an ectoparasite infestation on a small ruminant or companion animal, comprising topically applying to the hair and/or skin of the animal a formulation of Claim 1, 2, 3, 4, 5, 6, 7, or 8.

11. The method of Claim 10 wherein the formulation is applied using a spot-on protocol.

12. The method of Claim 10 wherein the formulation is applied using a pour-on protocol.

13. A topical ectoparasiticidal formulation comprising from about 0.1 to about 25 weight percent of an ectoparasiticide, from about 25 to about 99.9 weight percent of a (C_3-C_6) branched alkyl (C_{10}-C_{20}) alkanoate spreading agent, and optionally up to about 70 weight percent of a miscibilizing agent compatible with organic solvent systems, substantially as hereinbefore described with reference to any one of the Examples.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 00/19549

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 128 351 A (BAYER) 19 December 1984 (1984-12-19) claims 4,6 page 23; example 3 page 25; example 9 ---	1-3,5, 9-13
X	EP 0 069 269 A (BAYER) 12 January 1983 (1983-01-12) claim 1 page 5, line 5 -page 7, line 15 page 11; example 1 --- -/--	1-3,6,7, 9-13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 November 2000	07/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ventura Amat, A

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/19549

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 198721 Derwent Publications Ltd., London, GB; AN 1987-145349 XP002153469 & HU 41 238 A (NEHEZVEGYIPARI), 28 April 1987 (1987-04-28) abstract	1-3,9-13
X	CHEMICAL ABSTRACTS, vol. 102, no. 3, 21 January 1985 (1985-01-21) Columbus, Ohio, US; abstract no. 19640, KIERAN, PETER JOHN ET AL: "Pour-on formulation for lice control" XP002153466 abstract & AU 83219 47 A (WELLCOME AUSTRALIA LTD., AUSTRALIA) 12 April 1984 (1984-04-12)	1-3,5, 9-13
X	CHEMICAL ABSTRACTS, vol. 101, no. 11, 10 September 1984 (1984-09-10) Columbus, Ohio, US; abstract no. 85712, KIERAN, PETER JOHN ET AL: "Pyrethroids for combatting sheep ectoparasites" XP002153467 abstract & AU 82918 50 A (WELLCOME AUSTRALIA LTD., AUSTRALIA) 24 March 1983 (1983-03-24)	1-3,5, 9-13
X	CHEMICAL ABSTRACTS, vol. 100, no. 7, 13 February 1984 (1984-02-13) Columbus, Ohio, US; abstract no. 47094, KIERAN, PETER JOHN ET AL: "Control of sheep lice" XP002153468 abstract & AU 81770 04 A (WELLCOME AUSTRALIA LTD., AUSTRALIA) 27 May 1982 (1982-05-27)	1-3,5, 9-12
P,X	WO 00 29378 A (NOVARTIS) 25 May 2000 (2000-05-25) claims 22,25 page 11, paragraph 7 -page 15, paragraph 1 page 82; example 5	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/US 00/19549

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 128351 A	19-12-1984	DE 3317823 A	22-11-1984
		AU 2806384 A	22-11-1984
		DK 241184 A	18-11-1984
		GR 82066 A	13-12-1984
		HU 34721 A	28-04-1985
		JP 59212403 A	01-12-1984
		PH 19050 A	11-12-1985
		ZA 8403680 A	24-12-1984
EP 69269 A	12-01-1983	DE 3125897 A	10-02-1983
		AT 21478 T	15-09-1986
		AU 560431 B	09-04-1987
		AU 8546682 A	06-01-1983
		DE 3272717 D	25-09-1986
		DK 294882 A	02-01-1983
		JP 1013681 B	07-03-1989
		JP 58008002 A	18-01-1983
		NZ 201086 A	11-04-1986
		PH 18948 A	14-11-1985
		ZA 8204663 A	27-04-1983
HU 41238 A	28-04-1987	NONE	
AU 8321947 A		NONE	
AU 8291850 A		NONE	
AU 8177004 A		NONE	
WO 0029378 A	25-05-2000	AU 1553100 A	05-06-2000